REMARKS

Status of the claims

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-61 are currently pending in the application and stand rejected. No claims are amended.

The 35 U.S.C. §103 rejection

Claims 1-2, 4-5, 8, 10-11, 49, 51-53 and 59-60 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* (Cancer Biotherapy & Radiopharmaceuticals 2000, 15:235-244) in view of **Satoh** *et al.* (Eur. J. Cancer Clin Oncol. 1989; 25:1727-1731), **Jones** *et al.* (Nuclear Medicine & Biology 1996; 23:105-113) and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol. 1984; 107: 57-60) in further view of **Nair** *et al.* (J. Radiat. Res. 2001; 42: 21-37). The Applicants respectfully traverse this rejection.

The Examiner states that **Kennel** *et al.* teach a method of treating lung cancer with alpha particles comprising administering ^{225}Ac bound to a HEHA-MAb 210B conjugate. The Examiner states that **Kennel** *et al.* further disclose that the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy. For example, **Kennel** *et al.* report at necropsy, animals had total ablation of bone marrow cells, splenic atrophy, some damage to the lining of their stomachs and intestine and excess accumulation of undigested food in their stomachs. The Examiner concedes that **Kennel** *et al.* do not explicitly teach administering a competitive metal blocker or a diuretic in combination with the ^{225}Ac conjugate.

The Examiner states that **Satoh** *et al.* teach the effects of preinduction of metallotheionein by bismuth subnitrate on the adverse effects and antitumor activity of γ-ray irradiation in mice. In particular, the Examiner states that **Satoh** *et al.* teach that oral administration of bismuth subnitrate markedly reduced the lethal effects and bone marrow damage by γ-ray irradiation without compromising the tumor-reducing effect. As such, **Satoh** *et al.* teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy.

The Examiner states that **Jones** *et al.* teach that a problem with the clinical use of 212Bi or 212Pb radioimmunoconjugates is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal. More particularly, **Jones** *et al.* cite that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radiometal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal binding proteins. The Examiner states that in order to overcome this limitation, **Jones** *et al.* disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicity of Lead-212 or Bismuth-212 alpha-radioimmunotherapy.

The Examiner states that **Schilcher** *et al.* teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors. The Examiner states that **Nair** *et al.* teach radioprotector in radiotherapy. More particularly, the Examiner states that **Nair** *et al.* teach that while acute toxicity has been a main reason for

radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the teachings of the references so as to modify the method of **Kennel** *et al.* to include administration of a metal blocker such as bismuths subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.* and **Schilcher** *et al.* Examiner further states that one would have been motivated to do so because each of the references teach that the agents are effective at reducing radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, one of ordinary skill in the art would have reasonable expectation of success that by modifying the method taught by **Kennel** *et al.* to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.* and **Schilcher** *et al.*, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney as well as bone marrow damage.

Furthermore, in response to Applicants' prior arguments, the Examiner states that Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a conjugate, wherein the radiotoxicity associated with ^{213}Bi accumulation in the kidneys limits the effectiveness of the therapy, while **Satoh** *et al.*, **Jones** *et al.* and **Schilcher** *et al.* each teach agents which are effective at reducing toxicities associated with

radiotherapies. Taking these references together, the Examiner states that one of ordinary skill in the art would have a rasonable expectation of success that by modifying the method taught by **Kennel** *et al.* to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide. Furthermore, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

With regards to **Schilcher** *et al.*, the Examiner acknowledges that the platinum in cisplatin is not a radiometal. However, the Examiner asserts that Applicants' argument pertaining to the differing mechanisms of action are moot without some type of evidence to suggest that the mechanisms of causing nephrotoxicity are different and that furosemide administration would result in a different effect. The Applicants respectfully disagree.

The Applicants submit that **Kennel** *et al.* disclose evaluation of Ac-225 for vascular targeted radioimmunotherapy of lung tumors and conclude that the potential for Ac-225 as radioimmunotherapeutic agent is compromised most prominently by the radiotoxicity associated with the decay daughter radioisotopes released from the target organ (Abstract). **Kennel** *et al.* further disclose that they know of no conventional chelate that could withstand the energy released by radioactive decay of Ac-225 (pg 243, col. 1, lines 2-4).

Satoh *et al.* disclose that the preinduction of metallothionein by oral administration of bismuth subnitrate may reduce the adverse effects of gamma ray irradiation in mice (Abstract). A dose of 200 mg/kg prior to irradiation with a lethal dose

of 6 Hy/leg of cobalt-60 suppressed leukocyte reduction and lipid peroxidation in bone marrow cells and increased metallothionein 2-fold therein (pg 1728, col. 2). It is assumed that bismuth subnitrate induces an increased level of metallothionein which scavenges the free radicals induced by the gamma irradiation and thereby protects the bone marrow from gamma radiation injury (pg 1729, col. 2 to pg 1730 col. 1, ll. 2).

Jones *et al.* disclose that 2,3-dimercapto-1-propanesulfonic acid (DMPS), which is more effective than DMSA, can be used as a potential adjuvant chelation therapy in lead-212 or bismuth-212 radioimmunotherapy protocols (Abstract). **Schilcher** *et al.* examines the effect of fractionated low and single high dose cisplatin in various tumors. **Schilcher** *et al.* state that cisplatin therapy was associated with nephrotoxicity (pg 59, col 2) and that cumulative nephrotoxicity was prevented by prehydration and/or treatment with furosemide or mannitol (Summary) although **Schilcher** *et al.* do not support this assertion with any actual data. In fact, nephrotoxicity associated with the cisplatin therapy was observed in only three patients (pg 59, col 1, 2).

Nair *et al.* review radioprotecting agents categorized as radioprotectors, adaptogens and adsorbents (pg 22) and hypothesize that using non-toxic amounts of several agents might overcome the toxicities associated with larger doses required when used individually (pg 31).

The Applicants respectfully submit that the combination of **Kennel** *et al.*, **Satoh** *et al.*, **Jones** *et al.*, **Schilcher** *et al.*, and **Nair** *et al.* does not render the claimed invention obviousness. First of all, **Kennel** *et al.* state clearly that the radiotoxicity of ^{225}Ac is a significant problem which precludes its use in clinical therapy. "The data

show that no dose could be determined which cured tumors but did not cause acute, lethal radiotoxicity" (pg 240, **Kennel** *et al.*). **Kennel** *et al.* conclude that "the potential for ^{225}Ac as a radioimmunotherapeutic agent is compromised not only by the slow release of ^{225}Ac from the HEHA chelator, but most importantly by the radiotoxicity associated with decay daughter radioisotopes released from the target organ" (abstract). Thus, it is clear that **Kennel** *et al.* view the radiotoxicity caused by ^{225}Ac to be a significant problem for which there is no obvious solution.

Secondly, while some of the references cited by the Examiner address ways to deal with radiotoxicity, the Applicants respectfully submit that the standard for *prima facie* obviousness has not been met. More specifically, there is no reasonable expectation of success from combining the references. None of the references cited deal with reducing radiotoxicity of ^{225}Ac. This is the critical problem which the claimed invention seeks to remedy, the very same problem stated in **Kennel** *et al.* For example, **Jones** *et al.* fail to mention the effectiveness of 2,3-dimercapto-1-propanesulfonic acid (DMPS) in reducing radiotoxicity resulting from ^{225}Ac administration. **Schilcher** *et al.* also fail to mention the effectiveness of furosemide in preventing radiotoxicity of ^{225}Ac administration. In fact, **Schilcher** *et al.* only mention furosemide in a single sentence in the abstract: "[c]umulative nephrotoxicity was prevented by prehydration and/or treatment with furosemide or mannitol." There is no teaching in **Schilcher** *et al.* regarding the dosage of furosemide to be administered nor any discussion on how effective the diuretic is in preventing nephrotoxicity. In fact, since Schilcher et al. is completely silent about the mechanism and the effectiveness of

furosemide, a person of ordinary skill in the art could have no reasonable expectation of success.

Lastly, the Applicants respectfully remind the Examiner that motivation to combine prior art teachings must be found in the references themselves and cannot be constructed using improper hindsight reasoning. The Applicants submit that there is no rationale in **Jones** *et al.* nor **Schilcher** *et al.* which would motivate a person of ordinary skill in the art to combine methods of reducing radiotoxicity of $^{212}Bi/^{212}Pb$ and cisplatin with Kennel et al. which teach ^{225}Ac radiotherapy.

Regarding the Examiner's response to prior arguments, the Applicants submit that the burden of proof is still on the Examiner because *prima facie* obviousness has not yet been established.

In view of the arguments presented, the Applicants respectfully request that the rejection of claims 1-2, 4-5, 8, 10-11, 49, 51-53 and 59-60 under 35 U.S.C. §103 be removed.

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al.* (US 2002/0058007) in view of **Satoh** *et al.* (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), **Jones** et al. (Nuclear Medicine & Biology 1996; 23: 105-113), and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol. 1984; 107:57-60) and in further view of **Nair** *et al.* (J. Radiat. Res. 2001; 42:21-37). The Applicants respectfully traverse this rejection.

The Examiner states that **Scheinberg** *et al.* teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically

effective dose of an ^{225}Ac conjugate comprising a functionalized chelate. The Examiner also states that various types of cancer including prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer are disclosed. With regards to the ^{225}Ac conjugate, the Examiner states that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. Moreover, the Examiner states that the toxicity of ^{225}Ac constructs, wherein histological analysis of deceased mice showed gastrointestinal musocal sloughing and bone marrow hyplasia, consistent with severe radiotoxicity. The Examiner concedes that **Scheinberg** *et al.* does not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

The Examiner applies **Satoh** *et al.*, **Jones** *et al.*, **Schilcher** *et al.* and **Nair** *et al.* in the same manner as the previous rejection. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the references so as to modify the method taught by **Kennel** *et al.* to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** et al., **Schilcher** et al. and **Nair** et al. The Applicants respectfully disagree.

The Applicants infer that the Examiner inadvertently applied **Kennel** *et al.* when **Scheinberg** *et al.* is the reference cited. Accordingly, Applicants' response will be directed towards **Scheinberg** *et al.*

The Applicants submit that **Scheinberg** *et al.* teach a method of treating cancerous cells with alpha particles by administering ^{225}Ac comprising a functionalized chelant. More specifically, **Scheinberg** *et al.* also briefly disclose using HuM195 antibody and DOTA as the chelating agent. Furthermore **Scheinberg** et al. disclose that mouse treated with a dosage higher than 500nCi showed gastrointestinal mucosal sloughing and bone marrow hyplasia which is consistent with radiotoxicity.

The Applicants respectfully submit that the combined references do not render the claimed invention obvious. First of all, a person of ordinary skill in the art would not be motivated to combine the references because **Scheinberg** *et al.* only disclose that there are symptoms in the gastrointestine and bone marrow which are consistent with radiotoxicity. There is no mention of specific mention of toxicity in the kidney. There is no specific evidence of nephrotoxicity. Thus, a person having ordinary skill in this art would not be motivated to address the problem of nephrotoxicity when applying ^{225}Ac as taught by **Scheinberg** *et al.*

Secondly, as discussed supra, none of the other references mention the radiotoxicity of ^{225}Ac which is the subject matter of the claimed invention. Thus, the standard of prima facie obviousness has not been met since there is no reasonable expectation of success without any working examples dealing specifically with the reduction of radiotoxicity resulting from ^{225}Ac in kidneys.

In view of the arguments presented herein, the Applicants respectfully request that the rejection of claims 1-2, 4-5, 8-12, 49, 51-53 and 58-61 under 35 U.S.C. 103 be removed.

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** *et al.* (Science 2001; 294: 1537-1540) in view of **Satoh** et al. (Eur. J. Cancer Clin. Oncol. 1989; 25: 1727-1731), **Jones** *et al.* (Nuclear Medicine & Biology 1996; 23: 105-113) and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol. 1984; 107: 57-60) and in further view of **Nair** *et al.* (J. Radiat. Res. 2001; 42: 21-37). The Applicants respectfully traverse this rejection.

The Examiner states that **McDevitt** *et al.* teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate. The Examiner also states that recited cancers include prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regard to the ^{225}Ac conjugate, the Examiner states that the reference teaches that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. As an example, the Examiner cites the ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Furthermore, the Examiner states that the reference discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. daughter of ^{225}Ac, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs. The Examiner concedes that **McDevitt** *et al.* does not explicitly teach administering a diuretic such as furosemide, a dithiol chelate and a metal blocker such as bismuth subnitrate in combination with the ^{225}Ac conjugate.

The Examiner applies **Satoh** *et al.*, **Jones** *et al.*, **Schilcher** *et al.* and **Nair** *et al.* in the same manner as the previous rejection. Thus, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the method taught by **McDevitt** *et al.* to include the administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diurectic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.* and **Schilcher** *et al.* The Examiner contends that one would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, the Examiner states that as taught by **Nair** *et al.*, combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. The Examiner further asserts that one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by **McDevitt** to include administration of a metal blocker such as bismuth subnitrate, a chelator such as DMPS and a diuretic such as furosemide in view of the teachings of **Satoh** *et al.*, **Jones** *et al.* and **Schilcher** *et al.*, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

Lastly, the Examiner states that while the combination of references do not explicitly teach the diuretic inhibits reabsorption of Actium-225 daughters and prevents accumulation of Francium-221 and Bismuth-213 daughters in the kidney, the claimed "wherein" limitation has not been given any patentable weight since it simply express the intended result of the process step, e.g., administration of the diuretic in

combination a chelated actinium-225 radioimmunoconjugate, positively recited. The Applicants respectfully disagree.

The Applicants submit that **McDevitt** *et al.* disclose a method of targeting molecular-sized generators of alpha-emitting isotope cascades to the inside of a cancer cell using Actium-225 coupled to internalizing antibodies. The application of these constructs induced tumor regression and prolonged survival, without toxicity in a substantial fraction of animals tested.

The Applicants respectfully submit that the combined references do not render the claimed invention obvious. First of all, **McDevitt** *et al.* disclose that their method of administering a single dose of alpha particles can induce tumor regression without toxicity. Thus, a having ordinary skill in this art would have no reason to combine **McDevitt** *et al.* with methods which reduce radiotoxicity levels in kidneys.

Secondly, while **McDevitt** *et al.* do show a biodistribution plot which show the levels of ^{225}Ac daughters localized in the kidney, the data is from a single mouse. Furthermore, there is no mention of whether the dosage found in the kidney is toxic. Thus, once again, a person of common sense would have no motivation to search for a method of reducing toxicity in kidneys resulting from the administration of ^{225}Ac.

Lastly, as discussed supra, the other references fail to discuss the radiotoxicity resulting from ^{225}Ac administration. Thus, the standard of prima facie obviousness has not been met since there is no reasonable expectation of success without any working examples dealing specifically with the reduction of radiotoxicity resulting from ^{225}Ac in kidneys.

In view of the arguments presented herein, the Applicants respectfully request that the rejection of claims 1-2, 4-5, 8-12, 49, 51-53 and 58-61 under 35 U.S.C. 103 be removed. The Applicants submit that all pending claims are now in condition for allowance. This is intended to be a complete response to the Office Action mailed July 20, 2009.

If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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